Remarks

Claims 1-6, 10-13, and 15-20 were pending in the subject application. By this Amendment, claims 1-6, 10-13, and 15-20 have been cancelled, and new claims 21-45 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 21-45 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

A supplemental Information Disclosure Statement (IDS) is submitted herewith for the Examiner's consideration. The applicant requests that the references listed on the accompanying Form PTO/SB/08 be made of record in the subject application and that the Examiner's consideration of these references be made of record.

The applicant and the applicant's representative wish to thank Examiner Qian for the courtesy of the telephonic interview conducted with the undersigned on April 11, 2005, regarding the rejection under 35 U.S.C. §112, first paragraph. The remarks and amendments set forth herein are consistent with the substance of the interview and are believed to address the outstanding issues as discussed during the interview.

By this Amendment, claims 1-6, 10-13, and 15-20 have been cancelled, and new claims 21-45 have been added. Support for claim 21 can be found throughout the subject specification including, for example, at page 2, lines 25-26, of the subject specification. Support for claims 22, 27, 42, and 43 can be found, for example, at page 2, lines 4-6, and the claims as originally filed. Support for claims 23-25, 28-30, and 37-40 can be found, for example, at page 3, lines 25-31, of the specification, and the claims as originally filed. Support for claim 26 can be found, for example, at page 3, lines 3-6; and page 6, lines 28-30, of the specification, and the claims as originally filed. Support for claim 31 can be found, for example, at page 1, lines 25-31; page 2, lines 1-3, 7-10, and 14; page 5, lines 13-18, and the claims as originally filed. Support for claims 32-36 can be found, for example, at page 2, lines 10-21, of the specification, and the claims as originally filed. Support for claim 41 can be found, for example, at page 2, lines 25-27, of the specification. Support for claim 44

can be found, for example, at page 6, line 8, of the specification. Support for claim 45 can be found, for example, at page 5, lines 9-12, of the specification.

Claims 1-6, 10-13, and 15-20 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled. The applicant respectfully traverses and submits that the claims are fully enabled by the subject specification. As indicated above, claims 1-6, 10-13, and 15-20 have been canceled and new claims 21-45 have been added by this Amendment.

The cells, compositions, and methods of the claimed invention are reasonably enabled by the specification, as one of ordinary skill in the art would be able to make and use the invention without undue experimentation.

New claims 21-29 are drawn to conditionally immortal hematopoietic stem cells and compositions containing such cells. As discussed during the telephonic interview, "when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for non-enablement based on how to use" (emphasis added) MPEP 2164.01(c). In addition to the treatment of neurological disorders taught in the specification, conditionally immortal hematopoietic stem cells (HSC) are useful *in vitro* or *in vivo* for many of the same purposes as other HSC. For example, as taught at page 3, lines 30-31, and page 4, lines 1-3 of the specification, the conditionally immortal HSC can be expanded *ex vivo* under permissive culture conditions and exposed to non-permissive conditions for differentiation. The differentiated cells can then be used as a source of various blood cell types. Similarly, conditionally immortal HSC can be expanded in culture and the differentiated cells can be used as a source of hematopoietic proteins. The conditionally immortal HSC can be genetically modified and used as a source of heterologous gene products (see WO 92/11355; WO 93/18137, and U.S. Patent No. 5,958,767, which are cited at page 1, lines 18-23, and page 7, line 4, of the specification, and of record). HSC transplants are also routinely used to treat patients with cancers and disorders of the blood and immune system (such as leukemia).

The Jat *et al.* publications (*Mol. Cell. Biology*, 1989, 9(4):1672-1681; *Proc. Natl. Acad. Sci. USA*, 1991, 88:5096-5100) are submitted with the IDS that accompanies this Amendment. A description of conditional immortality and a suitable immortalizing gene is provided in the Jat *et al.*

publications, as well as U.S. Patent No. 5,688,692, and WO 97/10329, which are cited at page 4, lines 14-16, of the specification.

Independent claim 31 recites a method for treating a cognitive deficit associated with brain damage, comprising intracerebrally administering an effective amount of hematopoietic stem cells to a patient in need of such treatment, wherein said intracerebral administering results in improved cognitive function. The applicant respectfully submits that the scope of enablement provided by the subject specification is commensurate with the scope of claims 31-45. HSC and their progeny express phenotypic markers and/or have functional properties similar to neural stem cells (NSC) and differentiated neural cells, and therapeutic benefits of NSC and differentiated neural cells have been reported in the scientific literature.

Transplanted murine HSC were demonstrated to survive two weeks (the end point of the experiment) and express proteins specific for neurons (MAP-2; NeuN; NeuroD; TH; GABA) and astroglia (GFAP) in a mouse model of stroke (see Chopp *et al.* abstract, of record, and page 6, lines 16-27, of the specification). Some of the proteins produced by transplanted HSC in the mouse model are markers of neural cells and are intrinsically beneficial. Tyrosine hydroxylase (TH) is an important rate-limiting enzyme in biosynthesis of catecholamines including dopamine, catalyzing the conversion of L-tyrosine to L-DOPA, and is a marker for dopaminergic neurons and noradrenergic neurons. Gamma-aminobutyric acid (GABA) is an inhibitory neurotransmitter and is a marker for GABAergic neurons. Parkinson's disease, for example, is a dopamine deficiency disorder. Thus, treatment strategies include pharmacological dopamine replacement (drugs that increase dopaminergic activity) and replacement of lost dopaminergic neurons. Submitted with the IDS that accompanies this Amendment is the Daadi and Weiss publication (*J. Neurosci.*, 1999, 19(11):4484-4497); see column 1, first paragraph, for a discussion of TH and TH-producing cells. Disruption of neurotransmitter systems (including cholinergic and serotonergic systems) have been observed in Alzheimer's disease as well.

The following publications are submitted with the IDS that accompanies this Admendment. These publications provide evidence that HSC and their progeny express phenotypic markers and/or have functional properties consistent with neural stem cells (NSC) and differentiated neural cells:

1. Koshizuka *et al.* publication (*J. Neuropath. Exp. Neurol.*, 2004, 63(1):64-72). The Koshizuka *et al.* demonstrates significant functional recovery in mice having a spinal cord injury following transplantation of HSC. Transplanted HSC differentiated into glial cells (astrocytes) and neural precursors in the recipient spinal cord.

2. Priller I publication (*Nature Medicine*, 2001, 7(12):1356-1361). The Priller I publication indicates that transplanted bone marrow-derived hematopoietic cells are attracted to sites of CNS damage, differentiate into microglia, and microglial engraftment is enhanced by the neuropathology.

3. Priller II publication (*ACNR*, 2004, 3(6):11-13). The Priller II publication is a review paper discussing the therapeutic potential of bone marrow-derived stem cells.

4. Hess *et al.* publication (*Stroke*, 2002, 33:1362-1368). Hess *et al.* indicate that transplanted bone marrow-derived progenitor cells can differentiate into cerebral endothelial cells and NeuN-expressing cells after a cerebral infarction.

5. Goolsby *et al.* publication (*PNAS*, 2003, 100(25):14926-14931). Goolsby *et al.* indicate that bone marrow-derived cells having an HSC phenotype survive for long periods, migrate, and express genes consistent with neural cells when transplanted into the mouse brain (see pages 14930-14931 and Table 3).

Human HSC have a neural potential similar to murine HSC. The Weimann *et al.* publication (*PNAS*, 2003, 100(4):2088-2093), of record, shows that human bone marrow cells have the capability of forming effective neural cells in human adult brains. Hao *et al.* (*J. Hematother. Stem Cell Res.*, 2003, 12(1):23-32, abstract only) and Cogle *et al.* (*Lancet*, 2004, 363(9419):1432-1437, abstract only) are submitted with the IDS accompanying this Amendment. Hao *et al.* indicate that human HSC can express neural progenitor cell markers (nestin and BMP-2) *in vitro* and subsequently differentiate into astrocytes based on morphology and marker expression (GFAP and S100), and states "therefore, human hematopoietic stem cells may be an alternative resource for generation of neural stem cells for therapy of central nervous system defects resulting from disease or trauma." Cogle *et al.* indicate that transplanted human bone marrow-derived hematopoietic cells can differentiate into neurons, astrocytes, and microglia in a long-term setting (up to 6 years post-

transplant), and states that "transplantable human haemopoietic cells could serve as a therapeutic source for long-term regenerative neuropoiesis."

Although some of the publications submitted herewith were published after the application's U.S. filing date, they confirm the accuracy and sufficiency of the disclosure as set forth in the specification as filed. The experimental data described in these papers confirms the applicability of the claimed methods to human cells and human patients, with a reasonable expectation of success in improving a cognitive deficit. These papers provide no information that is necessary for making and using the invention that is not also taught in the specification or known to those skilled in the art at the time the application was filed.

The applicant respectfully submits that an application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. Furthermore, the teaching within the specification concerning the manner of making and using the subject invention must be taken as true unless the Patent Office can cite specific reasons to doubt the objective truth of the statements contained therein. *In re Marzocchi* 169 USPQ 367 (CCPA 1971). The applicant has addressed each of the issues relied on by the examiner to question the therapeutic benefit conferred by the claimed invention and, thus, its enablement. These issues included, among others, the phenotype(s) actually exhibited by HSC in the brain, the phenotype(s) exhibited by human HSC, and the therapeutic benefit conferred by intracerebral transplantation of these cells. Thus, the applicant respectfully submits that the subject specification enables the claimed cell-based transplantation methods.

Accordingly, the applicant respectfully submits that, given the teaching of the specification, one of ordinary skill in the art could make and use the claimed invention without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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